

Quantifying Resilience of Humans and other Animals

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All life requires the capacity to recover from challenges that are as inevitable as they are unpredictable. Understanding this resilience is essential for managing the health of humans and their livestock. It has long been difficult to quantify resilience directly, forcing practitioners to rely on indirect static indicators of health. However, measurements from wearable electronics and other sources now allow us to analyze the dynamics of physiology and behavior with unsurpassed resolution. The resulting flood of data coincides with the emergence of novel analytical tools for estimating resilience from the pattern of micro-recoveries observed in natural time series. Such dynamic indicators of resilience (DIORs) may be used to monitor the risk of systemic failure across systems ranging from organs to entire organisms. These tools invite a fundamental rethink of our approach to the adaptive management of health and resilience.

The capacity of animals to regulate critical parameters such as blood pressure, temperature, and glucose levels depends upon the functioning of organs and other subsystems, linked through an intricate web of hormonal and neural communication (Fig. 1). The resulting complex dynamical system faces a regime of challenges related to physical strain, food intake, infections, adverse events, and a range of other stressors. If systemic resilience -the capacity to bounce back to normal functioning- decreases, risks of morbidity and mortality increase. Here, we address the question of how such systemic resilience may be understood as a unifying construct and quantified objectively. To see the relevance of this, consider three societal issues where understanding of resilience of the system is essential for effective management: the pollinator crisis, industrial livestock production and frailty in humans. Each of these examples vividly illustrates the need to look beyond single factors and take an integrative approach to manage and measure systemic resilience.

The pollinator crisis is a term used to describe the decline of bees and other insects threatening pollination services on which the majority of our crops depend (1, 2). Causes of bee decline include parasites, exposure to pesticides, and a lack of appropriate flowers; but the roles of these and other

factors are heavily debated (3). The stakes are high, as illustrated by the turmoil over the EU ban on neonicotinoids, a novel class of crop protection pesticides that have become widely used in farming and horticulture (4). While pathogens and parasites are often regarded as prime suspects in bee declines, a less visible underlying driver may be an impairment of their immune systems induced by exposure to neonicotinoids or by lack of food, further complicated by impacts of neonicotinoids on the navigation and communication systems exacerbating food stress (3, 5). Testing effects of the separate drivers in isolation is insufficient to explain bee decline (3). Instead, we need to understand how multiple stressors act to shape resilience of these animals and the superorganisms into which they are organized as eusocial insects.

Industrial Livestock Production is associated with concerns regarding animal welfare (6) as well as human health risks arising from antibiotic resistant bacteria (7) and disease outbreaks (8-10). One problem is that the conditions that facilitate highly efficient production of meat, milk and eggs tend to come at a cost in terms of resilience of the animals (11, 12). This has led to dependency on systematic antibiotic application to prevent excessive morbidity and mortality. Strategies for moving away from this situation will require a more holistic view of animal health, addressing its multifactorial nature in an effective way. For instance, it is becoming clear that not only genetic make-up (12, 13) and feed composition (14), but also early-life conditions supporting the development and expression of important behaviors and the establishment of social relationships (15, 16) have an impact on health and survival (17-19). However, we lack a quantitative understanding of how these multiple factors interact to shape animal resilience.

Human Resilience is a focus of increasing interest in geriatrics, where indices of frailty are now being developed to mark the risk of cascading declines in function (20-23). For instance, in frail elderly, a fall may cause hip fracture, but also trigger subsequent mental deterioration, social isolation and eating problems, provoking a cascading transition into a weakened state. While normal aging eventually results in frailty loss of resilience can happen earlier in life too. If risk of systemic failure is high, patients may require intensive care. Not surprisingly, efforts to understand resilience in humans are relatively advanced in geriatrics and critical-care medicine (24), but the topic is also of great interest in psychiatry where the breakdown of resilience characterizes various disorders (25-27). In spite of these efforts, healthcare diagnoses and treatments still remain focused mostly on single issues (28). In the face of a broad range of public health challenges and an aging population, there is a strong demand for better ways of assessing human resilience and unraveling factors that contribute to it.

The idea that systemic resilience may be a useful concept to integrate the complex multifactorial character of health is supported by work on the nematode *C. elegans*. The lifespan of this tiny worm can vary from days to months, depending on factors such as genes, food, temperatures and toxic compounds. Experiments exploring the effects of such diverse factors (29) unequivocally point to the existence of a single integrating characteristic of the animals on which all stressors act and that ultimately shapes the risk of death from any proximate cause; an aspect we may call resilience (30).

Despite overwhelming evidence for its importance and vast literatures on relevant aspects, there is no common framework for understanding systemic resilience and guiding its management. This void may be due in part to the difficulty of quantifying resilience. As we will show, we are now in a position to change this situation radically as a result of two recent developments. First, a novel family of dynamical indicators of resilience has emerged, providing surprisingly generic risk markers for the collapse of complex systems ranging from financial markets and ecosystems to the climate system and physiological systems (24, 31-37). Second, the dynamic time series that such methods require are starting to be ubiquitously available for humans and livestock thanks to the rapid rise of technologies

for automated recordings. This holds the promise of an entirely new approach to quantifying and monitoring resilience of animals and humans.

The Concepts of Resilience and Tipping Points

While the concept of resilience may seem intuitively straightforward, it is worth noting that it has been used in different ways across scientific disciplines and also outside academia. The fact that it is used in fields as diverse as ecology, engineering, environmental sciences, social sciences, economics, and psychology may in part be explained the malleability of the concept (38). Resilience takes different meanings, depending on the context and the field in which it is used (39, 40). Nonetheless, definitions invariably relate to the ability of a system to maintain specific functions in the face of change (38).

The interpretation of resilience takes a special twist in systems that have a tipping point: a threshold at which a self-reinforcing mechanism propels a critical transition to a contrasting state (41, 42). Efforts to understand such sharp transitions have a long history. In physics, abrupt phase transitions such as freezing may occur even when variables such as temperature gradually change. Also, slow endogenous change may build up a tension that brings a system to a critical point for radical change (43). Nearly 50 years ago, the mathematician Rene Thom (44), created a framework called catastrophe theory to characterize some of the abrupt transitions that could occur in dynamical system. Though catastrophe theory lost favor because it was initially oversold, the mathematical framework is robust and is now recognized as relevant across a broad range of systems (42). Especially, in ecology, researchers recognized the potential for systems to reach a tipping point early-on. To capture the risk of such critical transitions, ecologists defined resilience as the capacity to tolerate disturbance without collapsing (<http://www.resalliance.org/>). As this ‘ecological resilience’ approaches nil, a critical transition can be invoked even by a tiny nudge (45). It is intuitively straightforward to see how the potential for critical transitions is relevant to organisms (Fig. 2) where aging, and stressors can reduce resilience of the healthy state. In ecology, traditionally, resilience (46) was thought of as the magnitude of the perturbation needed to actually cause the shift (‘push it over the ridge’ in the representation of Fig. 2). However, this view raises the question of whether such resilience might in some way be quantified without invoking the shift. This would allow detecting situations where special attention is needed to prevent an unwanted transition (e.g. falling into a depression (37)) or situations where ‘bad resilience’ of an unwanted state is dwindling to the point the that a small nudge could push it out of such a trap (e.g. recovering from a depression (37)).

Dynamic Indicators of Resilience

Borrowing from the literature in physics, it has been found that subtle changes in the dynamics of systems may often be used to quantify the proximity of a tipping point, and to allow steps to be taken to avoid the transition (or to encourage it, if the system is in an unfavourable state to begin with). The most important of those early warning indicators are based on the phenomenon of ‘critical slowing down’ (33). Phrased simply, slower recovery from small perturbations (e.g. recovery of mood upon a bad experience) is an indicator that the system is becoming fragile and a tipping point (e.g. into depression) may be near. In mathematical terms, critical slowing down happens in continuous-time systems, when the real part of the dominant eigenvalue of the Jacobian matrix of the linearized model about a steady-state tends to zero as a bifurcation point is approached. Although, there are transitions in dynamical systems that may not be characterized in this simple way (33, 47, 48), empirical studies

across widely different systems suggest that critical slowing down is a surprisingly generic indicator of reduced resilience (31).

The cause of critical slowing down can be seen in an intuitive way from stability landscapes (Fig. 2). As the basin of attraction becomes smaller and shallower, its slopes become less steep (Fig. 2 B vs A), implying that the return rate to equilibrium upon small perturbations becomes slower (Fig. 2 D vs C). In principle, measuring this requires an experimental perturbation. However, there is a way around that. All complex systems (including our body) are continuously subject to stochastic variations in external conditions. The effect of this natural regime of ‘perturbations’ can be used to infer loss of resilience from a change in the nature of fluctuations in the state of a system (31-33, 49, 50). Explaining the mathematical background of this universal principle would go beyond the scope of this review, but the essence can be grasped intuitively. Stochastic fluctuations in the state of a system in part reflect micro-recoveries from small natural perturbations. Therefore, as intrinsic recovery rate from perturbations becomes slower, fluctuations in the state will become overall slower, which can be seen from an elevated correlation between the state on subsequent moments, the so-called temporal autocorrelation, which tends to go hand-in-hand with an increase in variance (Fig. 2 F vs E) (31-33, 49, 50).

Changes in recovery rates and the associated temporal autocorrelations are not the only class of generic indicators of resilience. Many complex systems can be seen as networks of subsystems, and organisms are no exception to that rule (Fig. 1). In such systems, the capacity to bounce back from challenges implies a capacity to avoid a cascading collapse that brings the entire network down. It has been shown that in networks where the elements depend on each other (facilitative networks), a rising correlation between the fluctuation in the time series of different elements may indicate the risk of such a systemic collapse (31). This makes intuitive sense for organisms. Malfunctioning of one subsystem (e.g. inflammation) will affect the outcome of other subsystems (e.g. cognition and gait) more strongly if those other subsystems have a low resilience already. Thus, as individual elements become less resilient, sensitivity to fluctuations in the functioning of other elements increases, which may lead to a rising cross-correlation between the ups and downs in functioning of the different elements of the system (Fig 2 H) (37, 51). The network perspective also helps seeing why resilience is an emergent property and why changes in components will combine to shape systemic resilience of the organism as a whole.

It should be noted that, as indicators of critical slowing down relate to changing dynamics around equilibria, they cannot be linked in simple ways to resilience of systems characterized by cycles or chaotic dynamic. Critical transitions in such systems have a complex nature and are difficult to foresee (33). The heart and the brain are examples. Possible early warning signals for seizures and particular kinds of heart failure have been linked to phenomena in dynamical systems theory but remain challenging to pick up from data (52-54). Here, we limit ourselves to the relatively intuitive class of resilience indicators related to slowing down. Slowing down will not happen prior to all transitions and even if it does, it can be challenging to detect. On the other hand, the generic nature of this phenomenon implies a strikingly wide scope of potential applications. Indeed indicators of slowing down have been shown to signal the loss of resilience prior to critical transitions in systems ranging from populations of yeast (55, 56), zooplankton (57) and cyanobacteria (58) to complex systems such as the climate (59), tropical forests (60) and Neolithic societies (61).

In the framework of critical slowing down, the capacity of the system to bounce back upon perturbations can be reflected in three characteristics: *variance*, *temporal autocorrelation* (correlations between states on subsequent moments) and *cross-correlation* (between different elements of the system). We coin those indicators *Dynamic Indicators of Resilience* (DIORs) to contrast them to the

traditional static correlates of the condition or health of a system. While such static indicators have long dominated medicine and animal science, technological advances now allow for assessing such DIORs. An extensive practical guide to the methods used for analyzing indicators of resilience is published elsewhere (62) linked to a website with freely available open-source software tools.

Resilience of the Subsystems

One way to deal with the complexity of studying animals and humans is to view them as sets of subsystems linked through a web of fast (nervous system) and slower (autocrine, paracrine, endocrine systems) feedbacks. The links allow organs to work together to maintain vital parameters within safe limits (Fig. 1). Depending on the functional reserve (overcapacity) of organs and the effectiveness of their coordination, subsystems ranging from temperature to body-posture may run into disorder when challenged. Some subsystems may gradually lose their function. However, others are ‘tipping elements’ (63, 64) in the sense that failure has a sharp all-or-none character often associated to severe health problems (65) (Supplementary material Table 1).

A well-known example of a tipping element in humans is blood pressure. Pressure drops if a person suddenly stands up, but this is quickly sensed and corrected by contraction of blood vessels and increased pumping by the heart. If such rapid regulation fails, blood pressure in the head drops, resulting in a *syncope* (fainting) (24). There are also tipping elements that are not limited to our internal physiology. The mood system is an example. While depressed feelings are transient in most persons, for others stressful life events may trigger a state of clinical depression that involves disturbances in several other subsystems such as sleep and appetite, and from which recovery can be difficult (66, 67). The profoundness and irreversibility of such depressed states are in part due to a set of reinforcing feedback mechanisms. For instance, a depressed person is likely to encounter negativity in relationships, take less physical exercise, make less social contact and eat less healthily, all of which may deepen the depression (25, 68).

The microbiomes on which humans and animals depend are complex ecosystems in their own right, tightly linked to the host system in intricate ways. Just like wetlands (69), forests (70) and coral reefs (71) such microbiomes may tip to an alternative state. A well-known example is acute *rumen acidosis* in beef cattle (72). If animals are fed a high level of rapidly digestible carbohydrates, fermentation increases resulting in lower pH of the rumen (first stomach). This decrease can favour acid-tolerant bacteria that in turn produce more lactic acid that drives pH down even more, thereby potentially tipping the rumen into a highly acidic state causing a severe crisis and potentially leading to death (72, 73).

Shifts between alternative states are typically triggered by stochastic events, and can therefore never be accurately predicted. However, there are good reasons to expect that dynamic indicators of resilience (DIORs) may be used to aid risk assessments. In the human health literature, there are already various lines of evidence that slowing down of recovery may signal reduced resilience for a range of subsystems (Supplementary material, Table 2). For instance, subjects with a slow rise in blood pressure following exercise have a five times higher risk of ischemic stroke (74) and persons with a slow rate of recovery of blood pressure upon standing up are more likely to experience a syncope (faint) (75, 76). Similarly, in psychiatry slowness of mood change (reflected in elevated temporal correlation and variance of emotions) has been found to be indicative of the risk of falling into a clinical depression later (37, 77). Also, in a cohort of elderly rising temporal correlation and variance of self-reported mood and physical wellbeing increases with (independently assessed) frailty (78).

Resilience of the Network

Although assessing the risk of critical transitions in subsystems can be useful, the central challenge we wish to address is to find ways to assess systemic resilience of the whole. Could there be reliable generic ways to quantify systemic resilience? Measuring recovery rates upon health crises is an obvious angle. However, there is evidence that declining systemic resilience of the whole may also be reflected in measurable declines of resilience of a range of subsystems. For instance, overall mortality risk is correlated to longer recovery time in blood pressure upon standing up (79, 80) and also to slowness in the recovery of heart rate during the first minute after exercise (81), as well as hand grip strength, gait speed and a range of other frailty indicators (20).

It may seem surprising at first sight that so many different indicators correlate to the risk of all-cause death. However, this observation can also be interpreted as evidence that resiliencies of the components and of the whole are linked. Such coupling becomes particularly apparent during the process of aging. In most animals, beyond some age mortality risk rises exponentially with the years (29). For instance, in humans, starting around 30 years, the likelihood of death doubles roughly every eight years. This rising mortality risk reflects the loss of resilience with age which is inevitable, but does depend on genetic make-up, stressors and life-style (Fig. 3). The loss of resilience is of course not completely homogeneous across the body. Some subsystems often remain stronger and compensate in part for weakening of others. Nonetheless, there is a tendency for the whole and its subsystems to decline in concert.

Part of an explanation may be that stresses influencing parameters such as Reactive Oxygen Species (ROS), chaperon protein regulation, autophagy and the accumulation of senescent cells affect tissues throughout the organism (82-84). However, the network of mutual dependencies may also cause correlation between resilience of the parts, as malfunctioning of one subsystem (e.g. glucose regulation) can raise the stress on other subsystems (e.g. water balance by increased urinary output, cognition by glycation of proteins) causing them to deteriorate too. In addition, organisms have to distribute resources over subsystems, implying that increased demand from one system may go at the expense of others.

This view of organisms as complex adaptive networks has implications for our understanding of systemic resilience and for the possibilities of assessment. It may explain why resilience of the elements can be predictive of systemic resilience of the whole, but also suggests that rising correlation between the ups-and-downs of elements in a network might indicate an elevated risk of systemic failure (Fig. 2 H vs G) (31). So-far, few studies have addressed this possibility, although a recent study of a cohort of Italian elderly indeed revealed that correlation between self-reported mood and physical wellbeing does indeed increase with (independently assessed) frailty (78). In summary, there is emerging evidence that humans and animals may be seen as complex networks where systemic resilience can be assessed from DIORs that may be estimated directly from the interactive dynamics of vital parameters such as blood pressure, activity, temperature, postural balance and mood.

Managing Resilience

Although quantification of systemic resilience has long remained elusive, a long-standing literature documents the ways in which genes, lifestyle, diseases and other stressors affect healthy dynamic functioning. Indeed, while a systematic approach to managing resilience is missing, the different

knobs to turn are basically known. Chronic stress in animals and humans is perhaps the best-known condition that may undermine resilience. The body responds to stress through a suite of reactions that allow energy bursts for fight or flight reactions. When such a state becomes sustained for too long, the resulting 'allostatic load' causes wear and tear on the body (85). As a result, the reactive scope of the organism to mount an adequate response to challenges gradually erodes (86). Chronic stress is also one of the leading adverse life events that have been shown to increase the risk of mental disorders such as depression (87).

While the effects of prolonged stress on health have been long known, the mechanisms explaining the multifactorial nature of resilience with all its cross-linkages are only starting to be unraveled. One line of work is now revealing how stressors to the mood system may affect the immune system. For instance, experiments on monkeys reveal how upregulation of proinflammatory genes in response to perceived social isolation comes at the cost of impaired response to viral infectious challenge and increased risk of chronic disease and mortality (88). However, this is only one of many mechanisms that may help explain correlations between life conditions and the risks of morbidity and mortality. The complexity of this issue is well illustrated by work on the relationship between income and disease (85, 89). Numerous mechanisms contribute to the high disease burden of low-income groups, and malnutrition is one of the obvious elements (90). As inflammatory responses and post-response repair are costly in terms of energy and proteins, malnutrition limits the capacity to fend off disease. This mechanism is vividly illustrated by the sharp rise of active tuberculosis in human populations when food becomes limiting (90, 91). The cost of mounting an immune response in turn also affects further resilience of an organism. For instance, in bumblebees an experimentally induced immune response led to increased mortality if the animals were not allowed to increase their feeding rate to compensate for the increased energy costs (92). Lastly, the effects of poverty on systemic resilience may have a cognitive component. Worries related to decisions that could affect resources tend to impede overall cognitive functioning (93). This in turn affects the quality of other choices, potentially leading to further negative health effects (94).

Taking a health management perspective, an obvious way to promote resilience is to minimize stressors that undermine it. However, there is an interesting paradox. While strong challenges can damage an organism, many forms of moderate challenge are known to promote longevity. For instance, moderate caloric restriction tends to promote longevity in animals (95, 96). Similarly, while extreme physical activity can have negative effects (97) the life-extending effect of moderate to vigorous exercise is well documented (98). Indeed, the proverbial observation "if you don't use it you lose it" applies to many functional aspects. On the other hand, "what doesn't kill you makes you stronger" is too much of an extrapolation. For example, heat- and drought-stressed individuals of the Australian white-plumed honeyeaters lost weight and were less likely to be re-captured in the following spring, presumably because they died (99). On a cellular level, the dual effect of challenge on longevity has been linked to the effects of reactive oxygen species (ROS). While ROS can cause cellular damage, low levels of ROS triggered by challenges such as caloric restriction, hypoxia, temperature stress and physical activity may actually promote longevity by inducing an adaptive response (100). While such molecular insights are fascinating, moderate challenge may also help to maintain function in simpler ways. For instance, exercise in elderly helps maintain muscle strength (101) which is an essential asset for systemic resilience in many ways.

So-far, even the effects of single factors on resilience are often poorly understood (Fig. 3), let alone the full picture of how different mechanisms interact to shape systemic resilience (Fig. 1). One limitation of research into this issue is the fact that the dependent variable is typically life-span or mortality rates. This implies the need for large cohorts and limits the scope for experimental studies.

The possibility to quantify and monitor systemic resilience of live animals and humans dynamically would greatly enhance the power of studies considering the interactive effects of different drivers. Moreover, lifespan itself is an endpoint of limited value. In geriatric care, ‘adding life to years’ may often be more valued than ‘adding years to life’.

Prospect

The dazzling web of mechanisms that shape resilience may seem disappointingly complex. However, even if the details are not resolved, taking a resilience-based approach need not be complicated. It may seem challenging to choose between the many potentially relevant actions but the multi-factorial nature of resilience implies that the precise choice may actually not matter too much. Working on any of the plausibly related elements should often help. Take the three examples from the introduction. To halt the demise of pollinators, it will help to increase the availability of flowers in a landscape but also to reduce exposure to pesticides (3). To reduce premature morbidity and mortality of piglets, it will help to choose genetically more resilient varieties, but also to provide an enriched environment increasing their resistance to infectious challenge (102). To enhance systemic resilience of elderly, it will help to ensure a nourishing diet, but also to promote physical and mental activity (103). Often some aspects are more difficult or costly to manage than others, allowing strategic choices based on identification of the nature of the problem.

While, (for humans) caring about general health is broadly embraced, healthcare diagnoses and treatments still remain focused mostly on single issues (28). Singling out well-defined sources of illness remains important. However, many, if not most health issues are related to interactions involving multiple subsystems of the organism. This becomes vividly clear in cases where severe loss of resilience causes multiple failures to arise simultaneously. For instance, in dairy cows the onset of lactation may trigger symptoms ranging from infections and metabolic disorders to entire collapse. Similarly, in frail elderly a broad set of somatic, mood, cognitive and social problems tend to coincide. Clearly, such multimorbidity is the tip of the iceberg. A tightly knit web of subsystems shapes systemic resilience in all organisms.

The view of organisms as a complex adaptive network logically requires a holistic approach to managing resilience in animals and man. It is easy to forget that fixing a problem with medication or other specific treatment may carry the risk of reducing overall systemic resilience. The accumulation of chronic illnesses despite ever more sophisticated drugs and devices suggests that sustaining and restoring resilience should itself become a major activity. The novel possibilities to measure resilience may become a game changer in this respect. Herds of thousands of electronically marked dairy cows are routinely providing real-time monitoring of all individuals allowing early detection of deviations that hint at individuals that are not doing well (104). Similarly, wearable sensors are starting to allow remote monitoring of large groups of patients. Moreover, the general public is beginning to share data from their own wearable electronics for analysis and comparison online. The emergence of DIORs, the Dynamic Indicators of Resilience thus comes at a moment where a growing flood of data may help tip human and animal science from a reductionist to a systemic paradigm. Diagnoses could become based on analyses of network resilience including essential elements, ranging from the mood and social conditions to different somatic subsystems. Meanwhile, management could become more adaptive, monitoring effects throughout the network and retuning medication and other variables over longer trajectories. In short, the recent technological and theoretical advances invite a fundamental rethink of our approach to managing health and resilience.

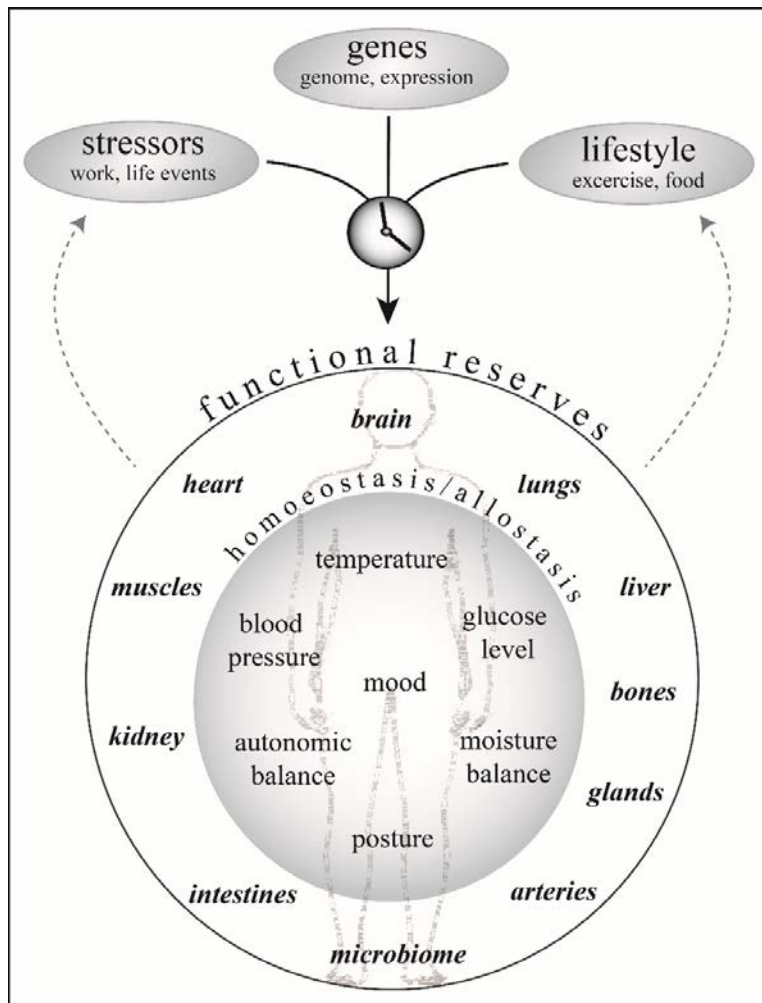


Fig. 1 The mechanisms that regulate systemic resilience in humans and animals.

Resilience of the whole depends on resilience of subsystems that regulate vital parameters such as temperature, glucose level, and mood. Those in turn depend among other things upon the functional reserves (overcapacity) of organs that inevitably wear down with aging, depending on stressors, life-style and genetic make-up.

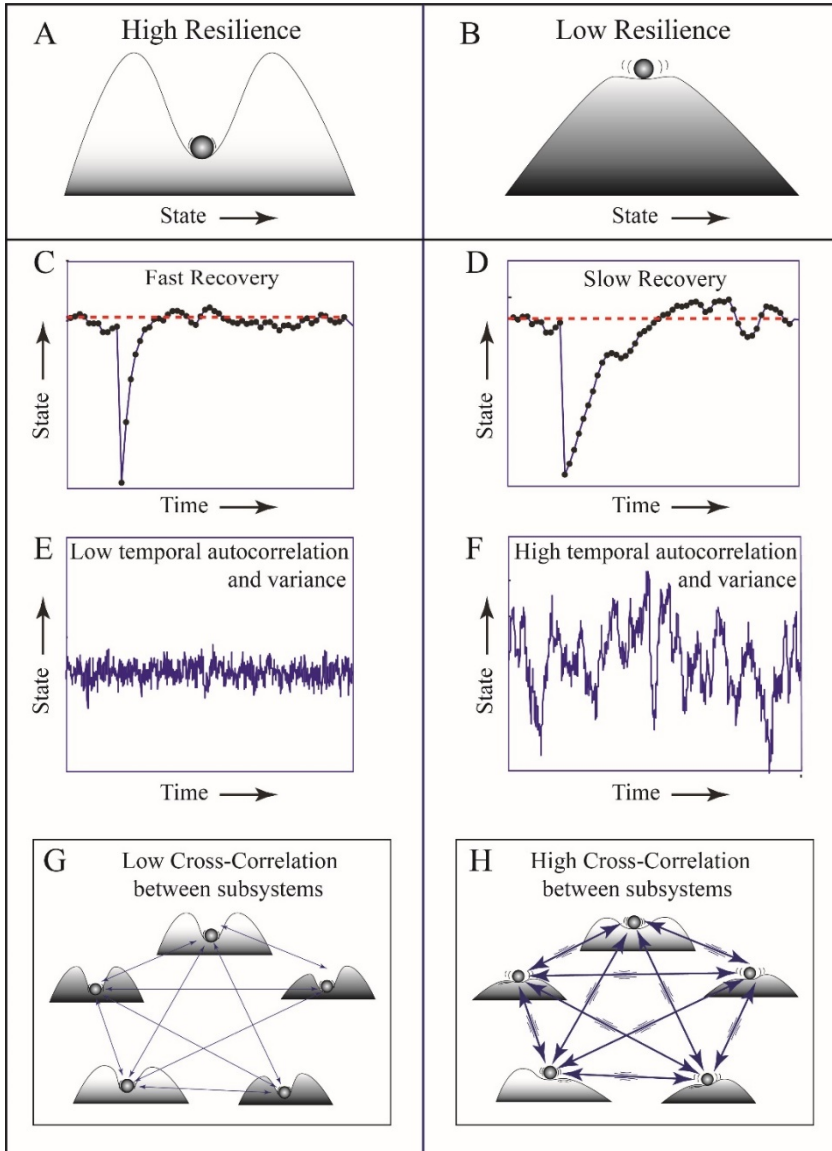


Fig. 2 Dynamic Indicators of Resilience (DIORs) discussed in the main text. Left hand panels represent a resilient system, right hand panels represent a frail system (with low resilience). Panels A and B: Resilience represented as the basin of attraction around a healthy state. Slopes correspond to rates of change. When resilience is low (B vs A), slopes around the equilibrium are less steep, implying slower return rates to equilibrium. Panels C and D: Simulated recovery rates upon a small perturbation. Panels E and F: Simulated dynamics in a system subject to a stochastic regime of perturbations illustrating that in a frail system (F vs E) fluctuations are larger and slower as reflected in higher variance and higher temporal autocorrelation. Panels G and H: Interactive dynamics of subsystems (e.g. mood, posture, cognition) are predicted to become more correlated in a network with low systemic resilience (H vs G).

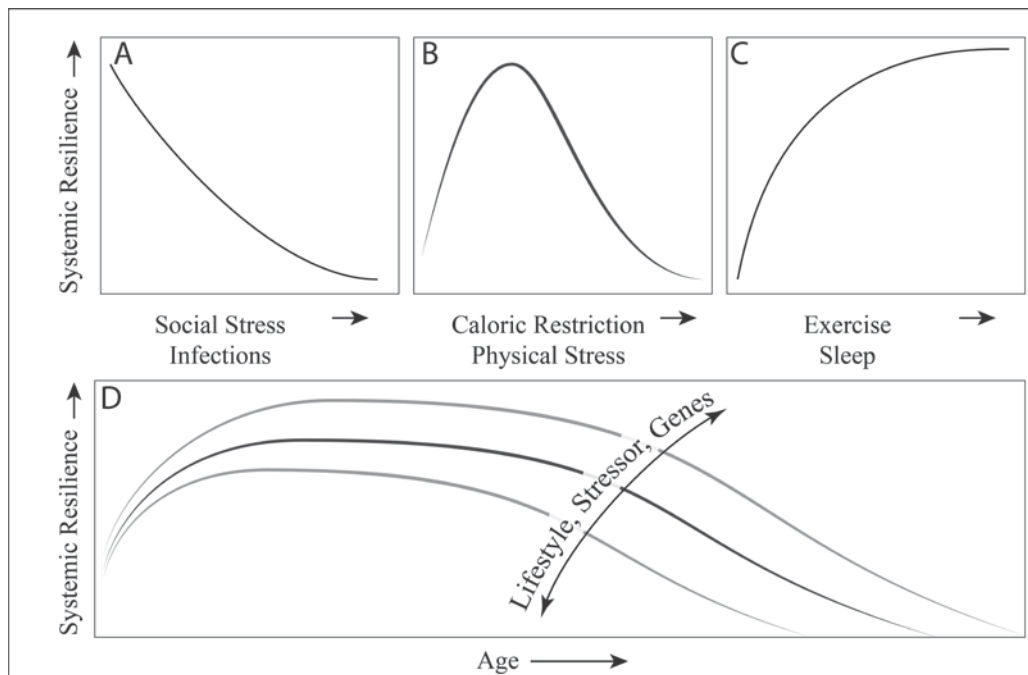


Fig. 3 Schematic representation of possible effects of different factors on systemic resilience.

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